FORM PTO-1390 (REV 10-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 33339/242753

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5): To be assigned 10/030500

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/DE00/02262	July 8, 2000	July 8, 1999

TITLE OF INVENTION

Vaccine Against Lentiviral Infections, Such As The Feline Immune Deficiency Virus Of The Cat

APPLICANT(S) FOR DO/EO/US

Christian Leutenegger; Mattias Schroff; Burghardt Willig; Hans Lutz

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).

4. ☐ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   - a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   - b. ☐ has been communicated by the International Bureau.
   - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☒ A English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).

7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   - b. ☐ have been communicated by the International Bureau.
   - c. ☒ have not been made; however, the time limit for making such amendments has NOT expired.
   - d. ☐ have not been made and will not be made.

8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. To 16. Below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information: International Preliminary Examination Report (German); Statement In Support Of Filing A Sequence Listing (Disk sent to U.S. Patent and Trademark Office, Box Sequence, P.O. Box 2327, Arlington, VA 22202 per Patent Office instructions).

10/030500 - 10/0305
531 Rec'd PCT/PTC 08 JAN 2002

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 10/030500 To be assigned	INTERNATIONAL APPLICATION NO. PCT/DE00/02262	ATTORNEY'S DOCKET NUMBER 33339/242753	
17. ☒ The following fees are submitted:		CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$1,040.00**		
International preliminary examination fee (37 CRF 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$ 890.00**	**$ 890.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search (37CFR 1.445(a)(2)) paid to USPTO	**$ 740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO But all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$ 710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	**$ 100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =		**$ 890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		**$ -0-**	
CLAIMS	NUMBER FILED / NUMBER EXTRA / RATE		
Total Claims	19 -20 = 0 X $18.00	**$ 0.00**	
Independent Claims	3 - 3 = 0 X $84.00	**$ 0.00**	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)	+ $280.00	**$**	
TOTAL OF ABOVE CALCULATIONS =		**$ 890.00**	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by one-half.		**$ -0-**	
SUBTOTAL =		**$ 890.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).		**$ -0-**	
TOTAL NATIONAL FEE =		**$ 890.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +		**$ -0-**	
TOTAL FEES ENCLOSED =		**$ 890.00**	
		Amount to be Refunded	**$**
		Charged	**$**

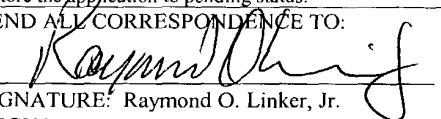
a. ☒ A check in the amount of $890.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 16-0605 in the amount of $ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 16-0605.

Note: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:



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Date of Deposit: January 8, 2002

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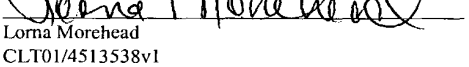

Lorna Morehead
CLT01/4513538v1

IN THE UNITED STATES DESIGNATED OFFICE (DO/US)

In re:	Leutenegger, et al.	Attn: DO/US
International Appl. No.:	PCT/DE00/02262	
International Filing Date:	July 8, 2000	
For:	Vaccine Against Lentiviral Infections, Such As The Feline Immune Deficiency Virus Of The Cat	

Box PCT
Commissioner for Patents
Washington, DC 20231

January 8, 2002

PRELIMINARY AMENDMENT

Sir:

Please amend the above-identified application as follows:

In The Claims:

1. (Amended) Vaccine for the protective vaccination or therapy of a lentivirus infection in *Felidae* comprising an immunising polynucleotide sequence which contains or consists of at least a part of the gene of a protein of the corresponding virus, particularly of the envelope protein (*env* gene), under the control of a eukaryotic promoter which is active in the corresponding animal.

2. (Amended) Vaccine in accordance with Claim 1 wherein the lentivirus is a lentivirus of an animal of the genus *Felidae*, specifically the domestic cat.

3. (Amended) Vaccine in accordance with Claim 2 wherein the lentivirus is the feline immune deficiency virus (FIV).

4. (Amended) Vaccine in accordance with Claim 1 wherein the immunising polynucleotide sequence contains a coding sequence which contains or consists of the extraviral or extracellularly situated domain of the *env* gene product, or a part of this.

5. (Amended) Vaccine in accordance with Claim 4 wherein the immunising polynucleotide sequence contains or consists of a coding sequence for at least twenty aminoacids of the transmembrane portion of the *env* gene product.

6. (Amended) Vaccine in accordance with Claim 1 which also contains at least one immunising section of the gene coding for an internal protein of the lentivirus.

7. (Amended) Vaccine in accordance with Claim 1 wherein the immunising polynucleotide sequence contains the coding sequence (SEQ ID NO. 4) of the plasmid sequence given under SEQ ID NO 1 or a sequence which is 85% identical with the coding sequence (SEQ ID NO 4) of the plasmid sequence given under SEQ ID NO 1, or a coding sequence which, without degeneration of the genetic code, is at least 85% identical with the coding sequence of the sequence given under SEQ ID NO 1.

8. (Amended) Vaccine in accordance with Claim 1 containing an accessory polynucleotide sequence which contains the sequences coding for IL-12 under the control of one or more eukaryotic promoters which are active in the corresponding animal.

9. (Amended) Vaccine in accordance with Claim 1 containing an accessory polynucleotide sequence which contains the sequence coding for IL-16 under the control of a eukaryotic promoter which is active in the corresponding animal.

10. (Amended) Vaccine in accordance with Claim 1 containing an accessory polynucleotide sequence which contains the sequence coding for IL-12 and IL-16 under the control of one or more eukaryotic promoters which are active in the corresponding animal.

11. (Amended) Vaccine in accordance with Claim 8 containing an accessory polynucleotide sequence which codes for both subunits of feline IL-12 and/or for feline IL-16 and wherein these sequences are under the control of a eukaryotic promoter which is active in the cat.

12. (Amended) Vaccine in accordance with Claim 8 containing an accessory polynucleotide sequence which contains at least one base sequence of the type $N^1N^2CGN^3N^4$, where N^1N^2 is an element of the group GT, GG, GA, AT or AA and N^3N^4 is an element of the group CT or TT.

13. (Amended) Vaccine in accordance with Claim 1 in which the immunising polynucleotide sequences and/or the accessory polynucleotide sequences are present as expression constructs which consist of linear and covalently capped molecules of desoxyribonucleic acid which contain a linear double-stranded region and in which the single strands which combine to form double strands are connected by short single-stranded loops of desoxyribonucleic acid and in which the single strands which combine to form double strands only consist of the coding sequence, a terminator sequence and a promoter which is active in the animal which is immunised.

14. (Amended) Vaccine in accordance with Claim 8 in which the accessory polynucleotide sequence contains a coding sequence in accordance with SEQ ID NO 8 (IL-12 p40), a coding sequence in accordance with SEQ ID NO 9 (IL-12 p35), coding sequences SEQ ID NO 10 (IL-16), SEQ ID NO 5 (CpG) or SEQ ID NO 6 (CpG) or a sequence which is complementary to one of these sequences.

15. (Amended) Vaccine for the vaccination or therapy of lentivirus infections in animals characterised by the presence of an immunising polynucleotide sequence and, in some cases, an accessory polynucleotide sequence in accordance with Claim 8, applied to a suitable massive and inert carrier material, in such a way that it can be accelerated into the skin of the animal, penetrate into the cells of the animal and be expressed there.

17. (Amended) Vaccine in accordance with Claim 15 which is characterised by the carrier material being gold.

18. (Amended) Vaccine for the protective vaccination or therapy of an infection with lentivirus in *Felidae* which is characterised by the fact that it contains an immunising protein or the envelope protein of the corresponding lentivirus, together with IL-12 and/or IL-16 in the form of protein.

REMARKS

The above amendments are made to more clearly define the invention under United States practice. Please enter this amendment prior to calculation of the filing fee.

Respectfully submitted,

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Date of Deposit January 8, 2002

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Lorna Morehead

Version With Markings to Show Changes Made:

1. (Amended) Vaccine for the protective vaccination or therapy of a lentivirus infection in *Felidae* [which has the characteristic that it contains] comprising an immunising polynucleotide sequence which contains or consists of at least a part of the gene of a protein of the corresponding virus, particularly of the envelope protein (*env* gene), under the control of a eukaryotic promoter which is active in the corresponding animal.

2. (Amended) Vaccine in accordance with Claim 1 [which has the characteristic that] wherein the lentivirus is a lentivirus of an animal of the genus *Felidae*, specifically the domestic cat.

3. (Amended) Vaccine in accordance with Claim 2 [which has the characteristic that] wherein the lentivirus is the feline immune deficiency virus (FIV).

4. (Amended) Vaccine in accordance with [Claims 1 to 3 which has the characteristic that] Claim 1 wherein the immunising polynucleotide sequence contains a coding sequence which contains or consists of the extraviral or extracellularly situated domain of the *env* gene product, or a part of this.

5. (Amended) Vaccine in accordance with Claim 4 [which has the characteristic that] wherein the immunising polynucleotide sequence contains or consists of a coding sequence for at least twenty aminoacids of the transmembrane portion of the *env* gene product.

6. (Amended) Vaccine in accordance with [Claims 1 to 5 which has the characteristic that it] Claim 1 which also contains at least one immunising section of the gene coding for an internal protein of the lentivirus[, for example the *gag* gene].

7. (Amended) Vaccine in accordance with [claims 1 to 6 which has the characteristic that] Claim 1 wherein the immunising polynucleotide sequence contains the coding sequence (SEQ ID NO. 4) of the plasmid sequence given under SEQ ID NO 1 or a sequence

which is 85% identical with the coding sequence (SEQ ID NO 4) of the plasmid sequence given under SEQ ID NO 1, or a coding sequence which, without degeneration of the genetic code, is at least 85% identical with the coding sequence of the sequence given under SEQ ID NO 1.

8. (Amended) Vaccine in accordance with [Claims 1 to 7 which is characterised by] Claim 1 containing an accessory polynucleotide sequence which contains the sequences coding for IL-12 under the control of one or more eukaryotic promoters which are active in the corresponding animal.

9. (Amended) Vaccine in accordance with [Claims 1 to 7 which is characterised by] Claim 1 containing an accessory polynucleotide sequence which contains the sequence coding for IL-16 under the control of a eukaryotic promoter which is active in the corresponding animal.

10. (Amended) Vaccine in accordance with [Claims 1 to 7 which is characterised by] Claim 1 containing an accessory polynucleotide sequence which contains the sequence coding for IL-12 and IL-16 under the control of one or more eukaryotic promoters which are active in the corresponding animal.

11. (Amended) Vaccine in accordance with [Claims 8 to 10 which is characterised by] Claim 8 containing an accessory polynucleotide sequence which codes for both subunits of feline IL-12 and/or for feline IL-16 and [that] wherein these sequences are under the control of a eukaryotic promoter which is active in the cat.

12. (Amended) Vaccine in accordance with [Claims 8 to 11 which is characterised by] Claim 8 containing an accessory polynucleotide sequence which contains at least one base sequence of the type $N^1N^2CGN^3N^4$, where N^1N^2 is an element of the group GT, GG, GA, AT or AA and N^3N^4 is an element of the group CT or TT.

13. (Amended) Vaccine in accordance with [at least one of Claims 1 to 12 which is characterised by the fact that] Claim 1 in which the immunising polynucleotide sequences and/or

the accessory polynucleotide sequences are present as expression constructs which consist of linear and covalently capped molecules of desoxyribonucleic acid which contain a linear double-stranded region and in which the single strands which combine to form double strands are connected by short single-stranded loops of desoxyribonucleic acid and in which the single strands which combine to form double strands only consist of the coding sequence, a terminator sequence and a promoter which is active in the animal which is immunised.

14. (Amended) Vaccine in accordance with [Claims 8 to 13 which is characterised by the fact that] Claim 8 in which the accessory polynucleotide sequence contains a coding sequence in accordance with SEQ ID NO 8 (IL-12 p40), a coding sequence in accordance with SEQ ID NO 9 (IL-12 p35), coding sequences SEQ ID NO 10 (IL-16), SEQ ID NO 5 (CpG) or SEQ ID NO 6 (CpG) or a sequence which is complementary to one of these sequences.

15. (Amended) Vaccine [in accordance with Claims 1 to 14] for the vaccination or therapy of lentivirus infections in animals characterised by the presence of an immunising polynucleotide sequence and, in some cases, an accessory polynucleotide sequence in accordance with [Claims 8 to 12] Claim 8, applied to a suitable massive and inert carrier material, in such a way that it can be accelerated into the skin of the animal, penetrate into the cells of the animal and be expressed there.

17. (Amended) Vaccine in accordance with [Claims 15 or 16] Claim 15 which is characterised by the carrier material being gold.

18. (Amended) Vaccine for the protective vaccination or therapy of an infection with lentivirus in *Felidae* which is characterised by the fact that it contains an immunising protein or [part of a protein, particularly] the envelope protein of the corresponding lentivirus, together with IL-12 and/or IL-16 in the form of protein.

Attorney's Docket No. 33339/242753

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Leutenegger, et al.	Attn: DO/US
International Appl. No.:	PCT/DE00/02262	
International Filing Date:	July 8, 2000	
For:	Vaccine Against Lentiviral Infections, Such As The Feline Immune Deficiency Virus Of The Cat	

BOX PCT
Commissioner for Patents
Washington, DC 20231

January 8, 2002

STATEMENT IN SUPPORT OF FILING A SEQUENCE LISTING UNDER 37 CFR § 1.821(f)

Sir:

I hereby state that the content of the paper and computer readable copies of the Sequence Listing, submitted concurrently herewith in accordance with 37 CFR § 1.821(c) and (e), are the same. The disk was mailed to U.S. Patent and Trademark Office, Box Sequence, P.O. Box 2327, Arlington, VA 22202, per Patent Office instructions.

Respectfully submitted,

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Attorney/Agent for Applicant
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"Express Mail" Mailing Label Number EL 822757774 US Date of Deposit: January 8, 2002 I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Box Patent Application, Commissioner for Patents, Washington, DC 20231. Lorna Morehead	**CERTIFICATE OF MAILING** I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner For Patents, Washington, DC 20231, on January 8, 2002.

SEQUENCE LISTING

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Schroff, Mattias
Willig, Burghardt
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01-10-02 10/030020

JC10 Rec'd PCT/PTO 08 JAN 2002 #4

Attorney's Docket No. 33339/242753 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Leutenegger, et al.	Attn: DO/US
International Appl. No.:	PCT/DE00/02262	
International Filing Date:	July 8, 2000	
For:	Vaccine Against Lentiviral Infections, Such As The Feline Immune Deficiency Virus Of The Cat	

U.S. Patent and Trademark Office
Box Sequence
P.O. Box 2327
Arlington, VA 22202

January 8, 2002

STATEMENT IN SUPPORT OF FILING A SEQUENCE LISTING UNDER 37 CFR § 1.821(f)

Sir:

I hereby state that the content of the paper and computer readable copies of the Sequence Listing, submitted concurrently herewith in accordance with 37 CFR § 1.821(c) and (e), are the same.

Respectfully submitted,

Raymond O. Linker, Jr.
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"Express Mail" Mailing Label Number EL 822757496 US Date of Deposit: January 8, 2002 I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to U.S. Patent & Trademark Office, Box Sequence, P.O. Box 2327, Arlington, VA 22202 Lorna Morehead	**CERTIFICATE OF MAILING** I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner For Patents, Washington, DC 20231, on January 8, 2002. _____

SEQUENCE LISTING

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Willig, Burghardt
Lutz, Hans

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Vaccination against Infections with Lentiviruses, such as Feline Immune Deficiency Virus in the Cat

Description

Scientific Area

The present invention is related to a DNA-based vaccine with which cats can be protected against the feline immune deficiency virus.

Scientific Status

In 1987 a virus was first isolated from domestic cats which leads to immune deficiency in infected animals (Pedersen et al., 1987). This is the feline immune deficiency virus (FIV), which, as a lentivirus, belongs to the group of the retroviruses. FIV is closely related to human immune deficiency virus (HIV), simian immune deficiency virus in monkeys (SIV), lentiviruses in horses (equine infectious anaemia virus, EIAV) and in small ruminants (Maedi-Visna virus in the sheep, MVV, and caprine arthritis encephalitis virus in the goat, CAEV), as well as bovine immune deficiency virus in the cow (BIV). Just as with HIV in man, FIV leads to a decrease in blood CD4 lymphocytes during the disease and to parallel increasing weakness in the immune system (Torten et al., 1991). When the number of blood CD4 lymphocytes has decreased below a certain level, the immune system fails totally, as a result of which the cats either die or have to be put to sleep. FIV-Infection occurs throughout the world, not only in domestic cats, but also in wild *Felidae*, such as lions in East Africa. However, the frequency of FIV infections in the domestic cat varies from country to country. In Switzerland, Germany and Austria, about 3-4% of sick cats which are taken to the vet are infected with this virus. In France and England and in some areas of the USA, the rate in sick cats is between 10 and 15%; in Japan, for example, it can be as high as 40%. FIV infection is thus an important disease which is of significance in veterinary medicine. However, aside from the veterinary aspect, FIV infection is also interesting for human medicine, as this infection is very similar to human infection with HIV and is therefore very suitable as a model for the study of HIV infection and its possible prevention and therapy (Gardner, 1991;

Jarrett et al., 1990). In their fight against FIV infection, vets and animal owners have until now been dependent exclusively on the detection of the infection by means of immunological tests and the separation of infected from non-infected animals. At the moment, there is no vaccination which facilitates the protection of cats against FIV infection without simultaneously inducing antibodies which lead to false positive reactions in the test used to detect FIV infection.

Natural protection against infectious diseases is based on the recognition by cells of the adaptive immune system of structures in pathogens which they have successfully combated. Two main activities may be distinguished here. On the one hand, there is the activity of the humoral immune system, which is based on the synthesis of antibodies by B-lymphocytes. On the other hand, there is the cellular immune system, which is based primarily on the activity of T-lymphocytes. These T-lymphocytes are capable of recognising body cells infected with viruses as "foreign". Depending on its specific function, the T-cell may then either amplify and modify the signal of recognition of foreign material (T helper cells), or directly initiate the lysis of the cell which has been recognised as foreign or infected (cytotoxic T-cells). Correct cooperation between the humoral and cellular immune systems is of decisive importance for the function of the immune response. In the last ten years it has become clear that the cellular arm of the immune response is induced by the activation of so-called type 1 helper cells and the humoral arm by activation of the so-called type 2 helper cells (Mosmann et al., 1986). In keeping with these names, the cellular arm is also known as the TH1 pathway and the humoral arm as the TH2 pathway of the immune system.

To solve these problems we had recourse to immunisation with DNA (Ulmer JB et al. 1993). This method has now been intensively researched and is based on vaccination with endogenously expressed antigens, which are processed intracellularly and presented to the immune system. In comparison with attenuated or recombinant vaccines, immunisation with DNA possesses not only technical and economic advantages, but also a series of biological advantages. In particular, these include the possibility of influencing the formation of a type 1 or type 2 response, either by co-expression of suitable cytokines or by insertion of substances which mediate signal transmission.

A series of procedures is known for the introduction of DNA expression constructs. The ballistic transfection of target cells is described in documents WO91/00539 and EP 0 500 799. Equipment for this is disclosed in WO95/19799.

Vaccination by direct injection of naked DNA is disclosed in US 5,580,859, US 5,589,466 and US 5,593,972.

A disadvantage of the vectors used at the moment for DNA immunisation is that either vectors of viral origin are used, which can result in safety problems (Gunzburg WH und Salmons B,1995), or plasmids are used. These must admittedly be regarded as absolutely safe from the epidemiological point of view and are greatly superior to viruses from the immunological point of view. They nevertheless contain sequences which make no contribution to the activity of the immunising expression cassette. These sequences include all those needed for replication in bacteria, such as the antibiotic resistance gene, replication origins etc. The problem is extensively discussed in WO98/21322.

Furthermore, the development of the immune response after DNA immunisation is highly dependent on the quantity and type of inoculated DNA. Depending on the method of introduction, the immunisation may require between <1µg DNA and >100µg DNA in the mouse. With larger quantities of DNA, the quality of the immune response can be greatly influenced by the presence of ISS (ISS = immunostimulatory nucleic acid sequences), such as CpG sequences (CpG = unmethylated cytosine-guanosine), in the ampicillin resistance gene. The ISS motives were indeed discovered by chance in an experiment to control this effect (Krieg et al. (1995)). If, for instance, the "gene gun" is used to introduce very small quantities of DNA into the patient's body for immunisation, a TH2 profile is typically found in the induced immune response. If, on the other hand, naked DNA is injected into muscle, much larger quantities of DNA are used and a TH1 profile is usually found.

It has been known for several years that certain short nucleic acid sequences included in the immuno-stimulatory ("ISS") nucleic acid sequences can exhibit considerable physiological activity in that they intensely stimulate the effector cells of the immune system through unknown mechanisms. These ISS are only a few bases long and do not act through proteins coded on them. Most known immuno-

modulatory short oligodesoxyribonucleotide sequences ("ODN") contain an unmethylated cytosine-guanosine motive (CpG motive). It is assumed that this motive is recognised in some unknown way in the eukaryotic cell and that this leads to a type of emergency mechanism which evokes a reaction to viral or bacterial pathogens (for a thorough discussion and further literature references see WO98/1810). It is suggested that these CpG motives are heavily suppressed in the eukaryotic genome in comparison with the prokaryotic genome, and that when they are recognised, this serves the higher animal as a "warning signal". According to this theory, the presence of the CpG motives signals an infection with prokaryotic pathogens and their recognition facilitates a response which is either independent of or occurs before the T-cell mediated immune response. The stimulation and proliferation of B-cells independently of T-helper cells is made possible by the provision by CpG-dependent signalling pathways of co-stimulatory signals which are necessary for T-cell and B-cell activation, such as the secretion of cytokines of the cellular type 1 response (TH1-specific **cytokines such as γ-interferon, IL-2 and IL-12). In addition, ISS leads** to increases in the activities of NK cells and macrophages. In contrast, the activity of type 2 cytokines (IL-4, IL-10) is suppressed, probably as a result of antagonism between the TH1 and TH2 responses (Lipford et al. 1997, Chu et al. 1997).

It has been postulated for HIV and other lentiviruses that the course of the infection is decisively influenced by the "decision" for a type 1 or type 2 response, which is evidently made very soon after contact with the virus (Romagnani et al., 1994). Thus groups of patients have been found in whom the blood count of CD4 helper cells remains high for a relatively long time and who have high levels of cytotoxic activity to HIV-specific antigens. An HIV-specific type 1 response has also been demonstrated for some patients who have probably come into contact with the virus but who nevertheless remain negative for HIV-antibodies. This has led to the idea that induction of a cytotoxic response to lentiviral antigens in the course of vaccination could prevent infection with the corresponding pathogens. However, this idea has not been proved, nor has a practical vaccine been found.

It is known from research with human HIV that the course of the infection of the target cells can be greatly influenced by the expression or blockade of certain chemokine receptors (Mackewicz CE, et al.1996). Moreover, it is thought that the expression of IL-16 can also contribute to the inhibition of HIV replication and could possi-

bly contribute to immunity in this way (Idziorek T, et al., 1998; Amiel et al.,1999; Zhou et al.,1997)

In spite of numerous attempts, there is at the moment no vaccine which can protect cats against this infection under field conditions and which does not interfere with the detection of the infection. It has been attempted to vaccinate cats against FIV by using FIV-infected cells which had been propagated in culture and inactivated with formalin before injection (Yamamoto et al., 1993; Yamamoto et al., 1991, see also Yamamoto: US 5,275,813, 4.1.94 and US 5,510,106, 23.4.96). Tompkins et al., US 5,413,927, describe a similar invention. Cats vaccinated in this way nevertheless developed antibodies to the different FIV virus proteins. These antibodies react with the diagnostic procedure which is now used (Tonelli, 1991), so that the test cannot be employed with such a cat to decide whether it is suffering from an infection or has been vaccinated. Several research groups have been trying for years to develop a vaccine which does not give a false-positive result with vaccinated animals and could thus be confused with an established FIV infection. The approach taken has been to examine vaccines based on the FIV envelope glycoprotein produced by genetic engineering, with suitable adjuvants. One of the inventors in the present application undertook the first experiments in this direction. No protection against a test infection was found, although the result suggested that the vaccinated animals were partially immune (Hofmann-Lehmann et al., 1995; Lutz et al., 1995). A later experiment led to clearly measurable partial immunity in one of the vaccinated groups (Leutenegger et al., 1998; Lutz et al., 1996). A further experiment was carried out in which cats were vaccinated with recombinant FIV envelope glycoprotein, which had previously been inactivated with formalin, together with lymphocytes. Different adjuvants for immunisation were investigated, but the experiments were not successful (Boretti and F., 1999). The work of other research groups on the use of recombinant envelope glycoprotein as vaccine antigen has been comprehensively documented (Huisman et al., 1998; Osterhaus et al., 1996; Richardson et al., 1997). These workers were also unsuccessful in achieving protection by using these envelope glycoproteins or the DNA which codes for it (Osterhaus et al., 1996; Richardson et al., 1997; Richardson et al., 1998).

Recombinant vaccines against FIV are also known from the patent of Wasmoen et al., US 5,849,303.

The use of IL-12 in man as adjuvant is known from US 5,571,515.

Instructions for the use and production of immuno-stimulatory, CpG-containing ISS is comprehensively explained in application WO 98/18810 and in the literature cited there.

Covalently capped dumb-bell shaped DNA expression constructs are described in Wittig et al. (WO 98/21322). Information disclosed in all documents mentioned should be regarded as part of the description presented here.

In spite of the many studies in this area, there is as yet no proven effective protective vaccine for cats against FIV.

The aim and intention of the present invention is therefore to prepare a vaccine for *Felidae* which is capable of inducing protection against illness after FIV infection. The vaccine should allow a distinction between vaccinated animals and diseased or infected animals on the basis of their antibody status.

Description of the Invention

According to the invention, this aim is achieved by immunising animals, particularly mammals such as cats, with a DNA sequence which codes for the envelope glycoprotein and also contains a part of the gene for the transmembrane protein. In a favoured embodiment of the invention, suitable adjuvants are added to the vaccine mixture to evoke a cytotoxic immune response. Examples of these adjuvants are the cytokines of the TH1 response, DNA expression constructs which code for cytokines and immuno-stimulatory DNA sequences.

To solve the problems described in the introduction, we had recourse to immunisation with DNA. This technique has already been discussed above (see e.g. Ulmer JB et al. (1993), WO91/00539, EP 500799, WO95/19799, US 5,580,859, US 5,589,466 and US 5,593,972).

The vaccine in the invention is intended for the prophylaxis or treatment of infections with lentiviruses, particularly FIV infections in the cat, and is characterised by the

presence of an immunising polynucleotide sequence, which contains or consists of at least a part of the gene of the envelope protein (*env* gene) of the corresponding lentivirus, particularly FIV. This must be under the control of a eukaryotic promoter which is active in the corresponding animal, particularly the cat. "At least a part of the gene of the envelope protein" means that one or more parts of this gene, or the whole gene, are present. The parts of the gene must be large enough to evoke an immune response.

Such a vaccine should preferably contain an immunising polynucleotide sequence for the domain of the *env* gene product which is extracellular or lies outside the virus, as well as a sequence which codes for at least 20 amino acids of the transmembrane section of the *env* gene product.

Nucleotide sequences which can be used in the present invention and which were used in the context of the embodiments may be found in the separate sequence protocol as SEQ ID NO 1 (FIV gp140), SEQ ID NO 2 (IL-12p40), SEQ ID NO 3 (IL-12p35), SEQ ID NO 4 (IL-16), SEQ ID NO 5 (CpG) and SEQ ID NO 6 (CpG).

The minimal section of the immunising polynucleotide sequence contained in a favoured vaccine may be the sequence given under SEQ ID NO 1, or a sequence which is at least 85% identical to that given under SEQ ID NO 1 or a sequence which is at least 85% identical to that given under SEQ ID NO 1 without degeneration of the genetic code. The similarity of the nucleic acids was calculated with the program MacMolly Complign Version 3.8 (www.mologen.com) and the parameters "gap penalty = 3" and "mismatch penalty = 1".

The sequences given above also include the complementary sequences.

In one embodiment of the invention the vaccine also includes at least one, or better two, accessory polynucleotide sequences. This accessory polynucleotide sequence includes the sequence which codes for IL-12. In particular, for the treatment of *Felidae*, specifically the domestic cat, this should be the sequence which codes for both subunits of feline IL-12, under the control of one or more eukaryotic promoters which are active in the corresponding animal. An additional or alternative possibility is to use the sequence which codes for IL-16. For the treatment of *Felidae*, specifically

the domestic cat, this should be the sequence which codes for feline IL-16. Again this must be under the control of an eukaryotic promoter which is active in the appropriate animal.

In a further embodiment of the vaccine, this can contain the sequence which codes for IL-12, for example the sequences which code for the two subunits of feline IL-12, and the sequence which codes for IL-16, for example the sequence which codes for feline IL-16, in the same accessory polynucleotide sequence, under the control of one or more eukaryotic promoters which are active in the appropriate animal, such as the cat.

In a further embodiment, the vaccine contains an accessory polynucleotide sequence, which includes the sequence $N^1N^2CGN^3N^4$ at least once, where N^1N^2 is an element of the group GT, GG, GA, AT or AA and N^3N^4 an element of the group CT or TT. As usual, C stands for cytosine, G for guanine, A for adenine and T for thymine. In the following embodiment, the 5'-phosphorylated oligodesoxynucleotides 5'-GTTCTTCGGG GCGTTCTTTT TTAAGAACGC CCC (SEQ ID NO 5) and 5'-GAAGAACGTT TTCCAATGAT TTTTCATTGG AAAAC (SEQ ID NO 6), in equimolar quantities and with a total DNA concentration of 1 mg per ml solution, were treated with T4 DNA ligase in the presence of 1 mm ATP. After ligation was complete, unconverted starting material was digested by reaction with T7 DNA polymerase in the absence of dNTPs and purified by anionic exchange HPLC to give the product.

Preferred sequences to be contained in the vaccine, specifically for the treatment of cats, are sequences in accordance with SEQ ID NO 2 (IL-12), SEQ ID NO 3 (IL-12), SEQ ID NO 4 (IL-16), SEQ ID NO 5 (CpG) or SEQ ID NO 6 (CpG).

The polynucleotide sequences or expression constructs, both the immunising and the accessory polynucleotide sequences, may consist of covalently capped linear desoxyribonucleic acid molecules, which include a linear double-stranded region and in which single strands incorporated into double strands are connected by short single-stranded loops of desoxyribonucleic acid nucleotides. These constructs preferably consist of only the coding sequence, under the control of a promoter which is active in the vaccinated animal and a terminator sequence.

A further object of the present invention is a procedure for the vaccination or treatment of infections with lentiviruses, particularly FIV infections in the cat, which has the particular characteristic that polynucleotide sequences as described above are applied to a suitable carrier, are accelerated, penetrate into the skin cells of the animal, specifically the cat, and are expressed there. A preferred carrier is gold, although other massive inert materials are also suitable.

Aside from the method described above for the use of vaccines with compositions in accordance with the invention, other modes of application can be used, in which the disadvantages mentioned in the discussion of the scientific status are at least partially reduced or preferably absent. These modes of application include, for example, administration of the polynucleotide sequences in aqueous solution by injection into the musculature.

As, according to current theory, the cytotoxic response is important and the development of this response should be provoked by efficient gene expression with as low as possible a contribution from inadvertently expressed proteins, the introduction of the vaccine by ballistic transfer of minimalistic DNA expression constructs is the currently favoured method of administration and is described in the following example.

The aim of the study carried out with ballistic transfer was, if possible, to differentiate the role of the components which make the essential protective contribution to the immune response. It is much more difficult to solve this problem in the cat than, for example, in man or in the mouse. With immunologically well researched species, much can be learnt about the underlying type of response by, for example, typing the antibodies formed in the course of the vaccination (IgG subtype 1 is specific to type 2 immune response, subtype IgG2b is specific to type 1). If the applicability of the type 1 / type 2 paradigm is assumed, this information allows conclusions about the efficacy and direction of a vaccination, even without a study on protection against infection. In this way it is possible to optimise the favoured composition and method of administration to achieve a hypothetically prophylactic immune response with much less effort than if each type of vaccination had to be examined with an experimental test of protection from infection In the present state of scientific knowledge, it is unfortunately not possible to make such predictions in the cat with the

same degree of confidence as would be the case with species such as the mouse or man. Even fundamental paradigms such as the type 1-type 2 dichotomy have not been demonstrated for the cat. There is a marked concordance between mouse and man in many fundamental immunological characteristics, but in many cases this is restricted to these two species and not transferable to others. This makes the great success of the regimen examined here even more surprising.

Vaccine according to the invention can, instead of polynucleotides, also contain proteins or glycoproteins which are coded by the nucleotide sequences described in the present application, e.g. in Example 1, or similar sequences. A vaccine experiment based on protein was described in detail by Leutenegger et al (1998). In this study a commercial adjuvant (QS-21) was used and the results were unsatisfactory, even though partial protection was achieved in some cats. The activity of vaccines based on proteins can be greatly amplified if protein cytokines (IL-12 and/or IL-16) are used as adjuvants, in accordance with the present invention. Proteins suitable for such vaccines include the proteins of FIV or immunising portions of these and the cytokines IL-12 and IL-16. These can be expressed in bacteria (e.g. E. coli), in yeasts, in mammalian cells (e.g. CHO cells), in insect cells (e.g. cells from Heliothis zea, ATCC No. CRL-9281), or in plants (e.g. tobacco), and then extracted and purified.

Further advantageous measures are included in the following sub-claims. The invention will now be further explained on the basis of figures and of a concrete embodiment, which should however in no way restrict the invention as defined in the claims.

Figure 1 shows the results of the quantification of FIV-RNA in cat plasma.

Embodiments

Five regimens for vaccination were formulated. The basic antigen in all groups, apart from the control group, was the gp140-SU antigen, which is the main product of the FIV *env* gene.

The gene construct mentioned here will be generally referred to as gp140-DNA. The following experiment was planned to test the usefulness of this gene construct. Six groups of 4 cats each were used and these were immunised with different preparations of gp140-DNA and, in some cases, DNA-coded adjuvants, or, in one case, non-coding adjuvant DNA. The DNA constructs were the above mentioned minimalistic expression constructs, consisting solely of a coding sequence preceded by the sequence of the cytomegalovirus promoter (CMV). The coding sequence and the CMV-promotor were used as linear double-stranded molecules, which were covalently capped at both ends to prevent extra- or intracellular degradation from exonucleases. The DNA constructs were adsorbed on small gold particles which were shot directly into the skin of experimental animals. The animals were bombarded with the corresponding constructs three times at intervals of three weeks; the DNA was applied to 1 mg gold per shot. Immunisation was carried out with a Helios gene-gun (Biorad, Munich, D) and a pressure of 500 psi. The total dose of DNA was 2 µg per animal per vaccination. Four weeks after the third vaccination, the animals were subjected to a test infection with the FIV strain which is used to prepare the vaccine antigen (Strain Zurich 2, (Morikawa et al., 1991)). The dose used for the test infection was 25 times the concentration which would cause infection in 50% of cats (cat infective dose 50 = CID_{50}). The groups were as follows:

Table 1 Composition of vaccine groups

Group No.	Vaccine contains:	Issue
1	Only gold particles	Negative controls, no protection expected for these cats
2	gp140-DNA	Efficacy of the gp140-DNA construct alone
3	gp140-DNA + IL-12-DNA	Additional activity of IL-12, in comparison with group 2
4	gp140-DNA + IL-16-DNA	Additional activity of IL-16, in comparison with group 2
5	gp140-DNA + IL-12-DNA + IL-16-DNA	Synergistic activity of IL-12 and IL-16 DNA, in comparison with Groups 3 and 4, respectively
6	gp140-DNA + CpG	Clarification of the effect of CpG,

The protection from the different vaccines was determined by measuring the following parameters at weekly intervals (Exception: The RNA loads were measured only in week 5):

1. Antibodies to the transmembrane protein (TM) were determined by an ELISA procedure.

2. The plasma load of FIV RNA was determined with a TaqMan®-PCR procedure.

3. The amount of FIV-DNA which is incorporated into lymphocyte DNA, the so-called provirus-DNA, was determined with a TaqMan® procedure (Leutenegger et al. 1999).

The results can be summarised as follows:

1. *Seroconversion against TM:* The course of the seroconversion is summarised in Table 2.

   It can be seen here that the animals in Control Group 1 seroconverted extraordinarily strongly, which suggests that the rate of virus replication is high. From the fifth week, four out of four animals in this group were seropositive.

   In Group 2, seroconversion occurred only gradually and the degree of seroconversion was much lower than in Group 1. Even in the ninth week not all animals in Group 2 were seropositive. This suggests that there is less virus replication, which is compatible with protection.

   In Group 3 only one animal seroconverted by the seventh week and the others remained fully negative. This suggests that three of the four animals were completely protected. The seroconversion in the single animal was low in comparison to the animals in Group 1, which suggests that there is only moderate virus replication.

In Group 4 two of the four animals seroconverted by the seventh week. Here too, only low levels of antibodies were formed, which also suggests that there are only low levels of virus replication. The combination of IL-12 and IL-16 in Group 5 turned out not to be effective against seroconversion. Four of the four animals had seroconverted by the seventh week.

The same applies to Group 6 as to Group 5. Here too, four of the four animals had seroconverted by the seventh week.

Table 2 FIV Vaccine Experiment, TM-ELISA Results

		Weeks after Test Infection												
Cat	**Group**	**-7**	**-5**	**-3**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**
2916	1	0.7	0	0	0	0.3	0.1	0	1.6	70.9	92.2	86.2	85.9	85.9
2932		1.2	0.3	0.2	0	0.8	0.4	0	1.6	59.8	78.6	96.2	65.6	65.6
381		0.6	1.3	0.1	0	0.4	0.2	0	5.3	78	95.3	72.6	89.3	89.3
384		0	1	0.1	0	0.4	0.7	0	10.7	83.8	90.7	78.7	79.4	79.4
2924	2	0	0.3	0	0	0.04	0.8	0.4	1.9	76.4	94.3	88.7	88.3	88.3
2947		0	1	0.5	0	0.4	0.6	0	0	0.4	1.3	0	60.4	60.4
379		0.6	0.9	0.1	0	0	0.4	0	0.4	0.8	16.7	31.6	82.4	82.4
393		0	0.3	0	0	0	0	0	0.8	66.7	85.7	63.6	90	90
2917	3	0	1.2	0.2	0	0	0.2	0	0	0.1	1.1	0	0.9	0.9
2943		0	0.8	0	0	0	0.8	0	0	0	0.9	0	0.8	0.8
377		1	2.4	2.3	0	2.6	0.4	0	1.6	0	2.1	0	0.5	0.5
388		0	0.2	0	0	0.4	0.1	0	0	54.6	86.6	68.8	80.1	80.1
2922	4	0	0.5	0	0	0.5	0	0	0	0	2.6	0	1.1	1.1
2933		0	0.7	0	0	0.3	0.1	0	0	6.7	88.2	86.6	80.4	80.4
382		0.7	1.4	1.4	0	0	0.7	0	1	0.1	1.4	3	64.3	64.3
394		0.2	1	0.4	0	0	0.3	0	0.4	0.05	39.9	45.7	74.6	74.6
2923	5	0	0.2	0	0	0	0.2	0	0.9	2.6	49.4	41.3	74.4	74.4
2959		0.08	0.6	0	0	0	0.3	0	47.5	88.5	97.2	93.4	79.1	79.1
378		0.4	1.9	0.2	3.6	0	0.3	0	2.9	50	99.2	77.4	81.6	81.6
389		0.08	0,2	0	0	0	0.2	0	0.3	38.3	89.4	73.3	97.8	97.8
2925	6	0.08	0.6	0	0.8	0	0.1	0	5	63.1	80	68	79.4	79.4
2936		0.3	1.2	0.2	0	0	0.4	0	0	8.1	61.2	64.2	60.2	60.2
380		1.4	7.4	0.1	0	0	0.4	0	0	1.3	70.3	56.8	71.8	71.8
385		1.6	9.5	1.2	0	0.7	0.2	0	1.3	9.7	108.3	65.4	87.2	87.2

2. *FIV-RNA Virus load in plasma:* The results of the quantification of FIV-RNA in cat plasma are summarised in Figure 1. The comments on the results are as follows:

Group 1: The RNA virus load was highest here.

Group 2: The cats which had been vaccinated with gp140-DNA exhibited a significantly lower RNA virus load than the control animals. This allows the conclusion that the gp140 construct alone is capable of inducing partial protection. The results agree with the serology.

Group 3: Adding IL-12 to the gp140-DNA fully protected the cats against blood virus up to the fifth week. These results also agree with the serological observations.

Group 4: The addition of IL-16-DNA also led to impressive protection, as no viruses were detected in plasma up to the fifth week in this group.

Group 5: The addition of both IL-12 and IL-16 turned out to be less effective than either IL-12 or IL-16 alone. In the fifth week RNA was detected in the plasma of three out of four animals. However, the quantity was significantly lower than in the control cats in Group 1.

Group 6: Using CpG also gave partial protection, although small quantities of FIV-RNA were detected in all animals in the fifth week.

3. *Quantity of proviral DNA:* The results on the quantification of proviral DNA are summarised for all the cats in Table 3. The comments on the results are as follows:

Group 1: As with the serology and the measurements of RNA, the animals in Group 1 are evidently fully susceptible to the test infection.

Group 2: The animals in Group 2 were also provirus-positive without exception; the mean quantity of FIV proviruswas only slightly less than that in the control group.

Group 3: The quantity of proviral DNA was lowest in this group, just as was found with the serology and with the measurements of RNA. Only one of the four animals was provirus-positive; the other three were not infected at all.

Group 4: IL-16-DNA too led to a lowered provirus load. Even in the sixth week this was significantly lower than in the control animals.

Group 5: Astonishingly, the provirus load was very low in animals which had been given a combination of IL-12 and IL-16. This allows the conclusion that IL-12 and IL-16 together provide significant protection against the integration of provirus into host DNA.

Group 6: Equally surprisingly, the effect of CpG addition on the quantity of provirus was also extremely marked. Only traces of integrated provirus could be detected in the sixth week. These results are somewhat in contradiction to the findings with the RNA measurements. They could perhaps be explained if the CpGs assist in inhibiting the integration of the virus into host DNA.

Table 3 *Provirus load in the individual cats*

Vaccine	Cat	Test Infect.	Week1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	Week 10
Gold	2916Y	0.00	0.00	0.00	0.00	720.65	2036.35	3250.62	2150.45	617.83
	2932Y	0.00	0.00	0.00	0.00	471.70	736.38	11649.83	490.65	570.69
	0381Y	0.00	0.00	0.00	0.00	1674.35	5853.32	9818.22	1676.30	2080.08
	0384Y	0.00	0.00	0.00	0.00	114.12	796.11	9393.60	9042.02	1570.48
gp140	2924Y	0.00	0.00	0.00	0.00	1867.55	5395.20	6378.60	17906.93	2661.38
	2947Y	0.00	0.00	0.00	0.00	0.00	0.00	8782.45	949.53	711.82
	0379Y	0.00	0.00	0.00	0.00	0.00	0.00	7096.10	34.97	205.24
	0393Y	0.00	0.00	0.00	0.00	344.56	1470.99	6683.63	709.22	2449.24
gp140 IL-12	2917Y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	2943Y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	0377Y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	0388Y	0.00	0.00	0.00	-	4555.94	4644.27	451.29	429.79	263.25
gp140 IL-16	2922Y	0.00	0.00	0.00	0.00	132.90	0.00	0.00	0.00	0.00
	2933Y	0.00	0.00	0.00	0.00	1169.13	-	3495.44	2205.85	1856.62
	0382Y	0.00	0.00	0.00	0.00	0.00	0.00	2754.58	-	1747.65
	0394Y	0.00	0.00	0.00	0.00	0.00	-	1789.69	915.75	923.14
gp140 IL-12 / IL-16	2923Y	0.00	0.00	0.00	0.00	0.00	-	2347.99	-	3134.67
	2959Y	0.00	0.00	0.00	7.24	2493.99	525.81	0.00	581.62	501.54
	0378Y	0.00	0.00	0.00	8.84	352.15	696.76	517.04	0.00	240.05
	0389Y	0.00	0.00	0.00	0.00	-	3963.26	592.80	2307.76	462.34
gp140 CpG	2936Y	0.00	0.00	0.00	0.00	31.33	232.77	333.68	7.98	82.91
	2925Y	0.00	0.00	0.00	0.00	19.12	51.55	101.89	-	-
	0380Y	0.00	0.00	0.00	0.00	94.31	0.00	8.57	8.24	5.49
	0385Y	0.00	0.00	0.00	0.00	0.00	89.10	337.48	96.46	174.80

-: not determined

Taken together, the results allow the surprising conclusion that gp140-DNA administered with various additional components induces different degrees of protection. This protective effect is evident in decreased viral replication, which leads to less or to no seroconversion and/or less integration of viral DNA into the DNA of the host cell.

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Patent Claims

1. Vaccine for the protective vaccination or therapy of a lentivirus infection in *Felidae* which has the characteristic that it contains an immunising polynucleotide sequence which contains or consists of at least a part of the gene of a protein of the corresponding virus, particularly of the envelope protein (*env* gene), under the control of a eukaryotic promoter which is active in the corresponding animal.

2. Vaccine in accordance with Claim 1 which has the characteristic that the lentivirus is a lentivirus of an animal of the genus *Felidae*, specifically the domestic cat.

3. Vaccine in accordance with Claim 2 which has the characteristic that the lentivirus is the feline immune deficiency virus (FIV).

4. Vaccine in accordance with Claims 1 to 3 which has the characteristic that the immunising polynucleotide sequence contains a coding sequence which contains or consists of the extraviral or extracellularly situated domain of the *env* gene product, or a part of this.

5. Vaccine in accordance with Claim 4 which has the characteristic that the immunising polynucleotide sequence contains or consists of a coding sequence for at least twenty aminoacids of the transmembrane portion of the *env* gene product.

6. Vaccine in accordance with Claims 1 to 5 which has the characteristic that it also contains at least one immunising section of the gene coding for an internal protein of the lentivirus, for example the *gag* gene.

7. Vaccine in accordance with claims 1 to 6 which has the characteristic that the immunising polynucleotide sequence contains the coding sequence (SEQ ID NO. 4) of the plasmid sequence given under SEQ ID NO 1 or a sequence which is 85% identical with the coding sequence (SEQ ID NO 4) of the plasmid sequence given under SEQ ID NO 1, or a coding sequence which, without degeneration of the genetic code, is at least 85% identical with the coding sequence of the sequence given under SEQ ID NO 1.

8. Vaccine in accordance with Claims 1 to 7 which is characterised by containing an accessory polynucleotide sequence which contains the sequences coding for IL-12 under the control of one or more eukaryotic promoters which are active in the corresponding animal.

9. Vaccine in accordance with Claims 1 to 7 which is characterised by containing an accessory polynucleotide sequence which contains the sequence coding for IL-16 under the control of a eukaryotic promoter which is active in the corresponding animal.

10. Vaccine in accordance with Claims 1 to 7 which is characterised by containing an accessory polynucleotide sequence which contains the sequence coding for IL-12 and IL-16 under the control of one or more eukaryotic promoters which are active in the corresponding animal.

11. Vaccine in accordance with Claims 8 to 10 which is characterised by containing an accessory polynucleotide sequence which codes for both subunits of feline IL-12 and/or for feline IL-16 and that these sequences are under the control of a eukaryotic promoter which is active in the cat.

12. Vaccine in accordance with Claims 8 to 11 which is characterised by containing an accessory polynucleotide sequence which contains at least one base sequence of the type $N^1N^2CGN^3N^4$, where N^1N^2 is an element of the group GT, GG, GA, AT or AA and N^3N^4 is an element of the group CT or TT.

13. Vaccine in accordance with at least one of Claims 1 to 12 which is characterised by the fact that the immunising polynucleotide sequences and/or the accessory polynucleotide sequences are present as expression constructs which consist of linear and covalently capped molecules of desoxyribonucleic acid which contain a linear double-stranded region and in which the single strands which combine to form double strands are connected by short single-stranded loops of desoxyribonucleic acid and in which the single strands which combine to form double strands only consist of the coding sequence, a terminator sequence and a promoter which is active in the animal which is immunised.

14. Vaccine in accordance with Claims 8 to 13 which is characterised by the fact that the accessory polynucleotide sequence contains a coding sequence in accordance with SEQ ID NO 8 (IL-12 p40), a coding sequence in accordance with SEQ ID NO 9 (IL-12 p35), coding sequences SEQ ID NO 10 (IL-16), SEQ ID NO 5 (CpG) or SEQ ID NO 6 (CpG) or a sequence which is complementary to one of these sequences.

15. Vaccine in accordance with Claims 1 to 14 for the vaccination or therapy of lentivirus infections in animals characterised by the presence of an immunising polynucleotide sequence and, in some cases, an accessory polynucleotide sequence in accordance with Claims 8 to 12, applied to a suitable massive and inert carrier material, in such a way that it can be accelerated into the skin of the animal, penetrate into the cells of the animal and be expressed there.

16. Vaccine in accordance with Claim 15 which is characterised by the animal belonging to the genus of the Felidae, specifically the domestic cat.

17. Vaccine in accordance with Claims 15 or 16 which is characterised by the carrier material being gold.

18. Vaccine for the protective vaccination or therapy of an infection with lentivirus in *Felidae* which is characterised by the fact that it contains an immunising protein or part of a protein, particularly the envelope protein of

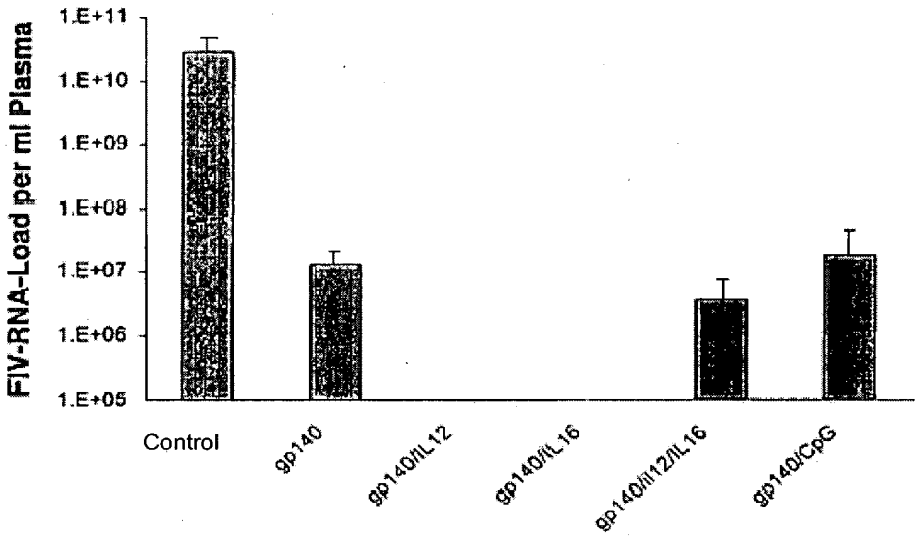
the corresponding lentivirus, together with IL-12 and/or IL-16 in the form of protein.

19. Procedure for the preparation of an immunising lentivirus protein or immunising parts of this, particularly of proteins or parts of proteins of FIV, which has the characteristic that a corresponding nucleotide sequence is expressed under the control of suitable expression sequences in the host cell and isolated from this.

ABSTRACT OF THE DISCLOSURE

A vaccine is described which is capable of inducing protection to disease consequent to an infection with lentivirus, in particular an infection with the feline immune deficiency virus (FIV), whereby the vaccination can be carried out in such a way that vaccinated animals can be distinguished from infected or diseased animals on the basis of their antibody status. A vaccine of this type includes a DNA sequence which codes for the envelope glycoprotein and preferably also contains a portion of the gene which codes for the transmembrane protein. A further aspect of the invention is that suitable adjuvants are included in the vaccine mixture which induce a cytotoxic immune response, for example cytokines of the TH1 Response, cytokine-coding DNA expression constructs or immuno-stimulatory DNA sequences.

FIV-RNA Load in Week 5



Declaration and Power of Attorney for Patent Application
Déclaration et Pouvoirs pour Demande de Brevet
French Language Declaration

En tant l'inventeur nommé ci-après, je déclare par le présent acte que :

As a below named inventor, I hereby declare that :

Mon domicile, mon adresse postale et ma nationalité sont ceux figurant ci-dessous à côté de mon nom.

My residence, post office address and citizenship are as stated next to my name.

Je crois être le premier inventeur original et unique (si un seul nom est mentionné ci-dessous), ou l'un des premiers co-inventeurs originaux (si plusieurs noms sont mentionnés ci-dessous) de l'objet revendiqué, pour lequel une demande de brevet a été déposée concernant l'invention intitulée

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed an for which a patent is sought on the invention entitled

VACCINE AGAINST LENTIVIRAL INFECTIONS, SUCH AS THE FELINE IMMUNE DEFICIENCY VIRUS OF THE CAT

et dont la description est fournie ci-joint à moins

the specification of which :

☐ ci-joint

☐ is attached hereto.

☐ a été déposée le

☒ was filed on **January 8, 2002**

sous le numéro de demande des Etats-Unis ou le numéro de demande international PCT

as United States Application Number **10/030,500** or PCT International Application Number

et modifiée le

and was amended on

(le cas échéant).

(if applicable).

Je déclare par le présent acte avoir passé en revue et compris le contenu de la description ci-dessus, revendications comprises, telles que modifiées par toute modification dont il aura été fait références ci-dessus.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

Je reconnais devoir divulguer toute information pertinente à la brevetabilité, comme défini dans le Titre 37, § 1.56 du Code fédéral des réglementations.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations,§ 1.56.

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French Language Declaration

Je revendique par le présent acte avoir la priorité étrangère, en vertu du Titre 35, § 119(a)-(d) ou § 365(b) du Code des Etats-Unis, sur toute demande étrangère de brevet ou certificat d'inventeur ou, en vertu du Titre 35, § 365(a) du même Code, sur toute demande internationale PCT désignant au moins un pays autre que les Etats-Unis et figurant ci-dessous et, en cochant la case, j'ai aussi indiqué ci-dessous toute demande étrangère de brevet, tout certificat d'inventeur ou toute demande internationale PCT ayant date de dépôt précédant celle de la demande à propos de laquelle une priorité est revendiquée.

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Prior Foreign application(s) Demande(s) de brever antérieure(s) dans un autre pays.			Priority claimed Droit de priorité revendiqué
1258/1999	**SWITZERLAND**	**8 July 1999**	
(Number) (Numéro)	(Country) (Pays)	(Day/Month/Year Filed) (Jour/Mois/Anné de dépôt)	☒ Yes / Oui ☐ No / Non
(Number) (Numéro)	(Country) (Pays)	(Day/Month/Year Filed) (Jour/Mois/Anné de dépôt)	☐ Yes / Oui ☐ No / Non

Je revendique par le présent acte tout bénéfice, en vertu du Titre 35, § 119(e) du Code des Etats-Unis, de toute demande de brevet provisoire effectuée aux Etats-Unis et figurant ci-dessous.

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application No.) (N° de demande)	(Filing Date) (Date de dépôt)

Je revendique par le présent acte tout bénéfice, en vertu du Titre 35, § 120 du Code des Etats-Unis, de toute demande de brevet effectuée aux Etats-Unis, ou en vertu du Titre 35, § 365© du même Code, de toute demande internationale PCT désignant les Etats-Unis et figurant ci-dessous et, dans la mesure où l'objet de chacune des revendications de cette demande de brevet n'est pas divulgué dans la demande antérieure américaine ou internationale PCT, en vertu des dispositions du premier paragraphe du Titre 35, § 112 du code des Etats-Unis, je reconnais devoir divulguer toute information pertinente à la brevetabilité, comme défini dans le Titre 37, § 1.56 du Code fédéral des réglementations, dont j'ai pu disposer entre la date de dépôt de la demande antérieure et la date de dépôt de la demande nationale ou internationale PCT de la présente demande :

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Application No.) (N° de demande)	(Filing Date) (Date de dépôt)	(Status) (patented, pending,abandoned) (Statut) (breveté, en cours d'examen, abandonné)
(Application No.) (N° de demande)	(Filing Date) (Date de dépôt)	(Status) (patented, pending,abandoned) (Statut) (breveté, en cours d'examen, abandonné)

Je déclare que par le présent acte que toute déclaration ci-incluse est, à ma connaissance, véridique et que toute déclaration formulée à partir de renseignements ou de suppositions est tenue pour véridique ;et de plus, que toutes ces déclarations ont été formulées en sachant que toute fausse déclaration volontaire ou son équivalent est passible d'une amende ou d'une incarcération, ou des deux, en vertu de la section 1001 du Titre 18 du Code de Etats-Unis, et que de telles déclarations volontairement fausses risquent de compromettre la validité de la demande de brevet ou du brevet délivré à partir de celle-ci.

I hebery declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

French Language Declaration

POUVOIRS : En tant que l'inventeur cité, je désigne par la présente l'(les) avocats(s) et/ou agent(s) suivant(s) pour qu'ils poursuive(nt) la procédure de cette demande de brevet et traite(nt) toute affaire s'y rapportant avec l'Office des brevets et des marquees : (mentionner le nom et le numéro d'enregistrement).

POWER OF ATTORNEY : As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to persecute this application and transact all bussiness in the Patent and Trademark Office connected therewith : (list name and registration number)

All practitioners associated with CUSTOMER NUMBER 000826

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Nom complete de l'unique ou premier inventeur	Full name of sole or first inventor
LEUTENEGGER Christian.	
Signature de l'inventeur: Date 10-5-02	Inventor's signature Date
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Nom complete du second co-inventeur, le cas echeant	Full name of second joint inventor, if any
2-00 SCHROFF Matthias	
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(Fournir les mêmes renseignements et la signature de tout co-inventeur supplémentaire.)

(Supply similar information and signature for third and subsequent joint inventors.)

French Language Declaration

Nom complete du troisième co-inventeur, le cas échéant WITTIG Burghardt	Full name of third joint inventor, if any
Signature de l'inventeur Date	Third inventor's signature Date
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Signature de l'inventeur Date Hans Lutz 10-5-02	Fourth inventor's signature Date
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Nom complete du cinquième co-inventeur, le cas echeant	Full name of fifth joint inventor, if any
Signature de l'inventeur Date	Fifth inventor's signature Date
Domicile	Residence
Nationalité	Citizenship
Adresse Postale	Post Office Address
Nom complete du sixième co-inventeur, le cas echeant	Full name of sixth joint inventor, if any
Signature de l'inventeur Date	Sixth inventor's signature Date
Domicile	Residence
Nationalité	Citizenship
Adresse Postale	Post Office Address

(Fournir les mêmes renseignements et la signature de tout co-inventeur supplémentaire.)

Supply similar information and signature for third and subsequent joint inventors.)